

10/031,795

Page 3

chain nodes :

7 8 9 10 11 14

ring nodes :

1 2 3 4 5 6 13 15 16 17 18 19 20

chain bonds :

7-8 8-9 8-11 9-10 13-14

ring bonds :

1-2 1-6 2-3 3-4 3-13 4-5 4-16 5-6 13-15 15-16 15-20 16-17 17-18 18-19 19-20

exact/norm bonds :

3-13 4-16 7-8 8-9 8-11 9-10 13-14 13-15 15-16 15-20 16-17 17-18 18-19 19-20

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6

G1:C,S

Match level :

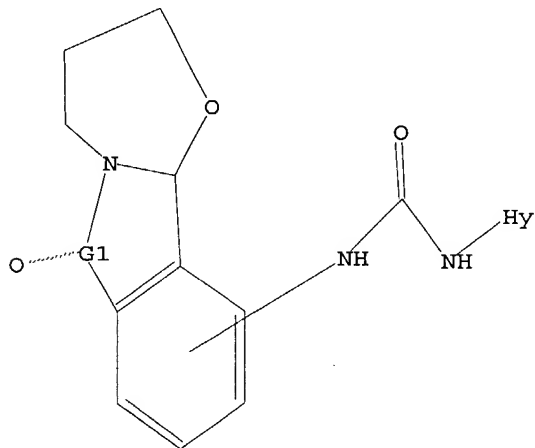
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:Atom
11:CLASS 12:CLASS 13:Atom 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom

L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR



G1 C,S

Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 10:43:47 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 1 TO ITERATE

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04/07/2004

10/031,795

Page 4

100.0% PROCESSED 1 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 1 TO 80
PROJECTED ANSWERS: 1 TO 80

L2 1 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 10:43:53 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 18 TO ITERATE

100.0% PROCESSED 18 ITERATIONS 18 ANSWERS
SEARCH TIME: 00.00.01

L3 18 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 155.42 155.63

FILE 'CAPLUS' ENTERED AT 10:43:58 ON 07 APR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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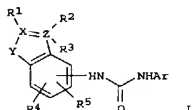
FILE COVERS 1907 - 7 Apr 2004 VOL 140 ISS 15
FILE LAST UPDATED: 6 Apr 2004 (20040406/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 2 L3
=> d ibib abs hitstr tot

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:591913 CAPLUS
 DOCUMENT NUMBER: 137:150215
 TITLE: Cdk4 and/or Cdk6 inhibitors with biaryl ureas and their salts as antitumor agents
 INVENTOR(S): Hatayama, Satoshi; Hayashi, Kyoko; Honma, Mitsuki; Takahashi, Ikuko
 PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 194 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002220338	A2	20020809	JP 2001-18755	20010126
PRIORITY APPLM. INFO.:			JP 2001-18755	20010126
OTHER SOURCE(S):		MARPAT 137:150215		



AB This invention relates to the general structures (I; Ar = N containing hetero aromatic ring, X, Z = C, etc.; Y = CO, etc.; R1-R5 = H, etc.) and their salts

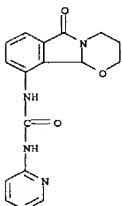
as Cdk4 and/or Cdk6 inhibitors. I have antiproliferative effects on cancer cells and are potential antitumor agents. Formulation examples of I capsules, tablets, and injections were given.

IT 322687-73-0 322687-74-1 322687-92-3
 322688-08-4 322688-09-5 322688-26-6
 322688-34-6 322688-35-7 322690-03-9
 445431-59-4 445431-64-1 445431-68-5
 445432-09-7

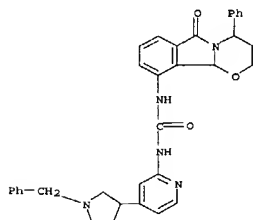
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOG (Biological study); USES (Uses)
 (Cdk4 and/or Cdk6 inhibitors with biaryl ureas and their salts as antitumor agents)

RN 322687-73-0 CAPLUS
 CN Urea, N-2-pyridinyl-N'-(3,4,6,10b-tetrahydro-6-oxo-4-phenyl-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)-(9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



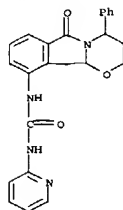
RN 322688-08-4 CAPLUS
 CN Urea, N-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]-N'-(3,4,6,10b-tetrahydro-6-oxo-4-phenyl-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)-(9CI) (CA INDEX NAME)



RN 322688-09-5 CAPLUS
 CN Urea, N-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]-N'-(3,4,6,10b-tetrahydro-6-oxo-4-phenyl-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)-(9CI) (CA INDEX NAME)

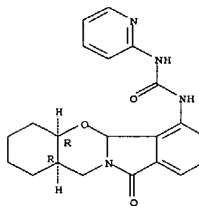
Absolute stereochemistry.

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



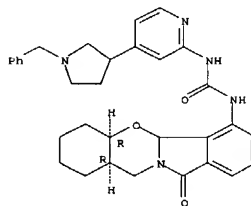
RN 322687-74-1 CAPLUS
 CN Urea, N-[(5aR,9aR)-4b,5a,6,8,9,9a,10,12-octahydro-12-oxo-7H-isoindolo[1,2-b][1,3]benzoxazin-4-yl]-N'-2-pyridinyl-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

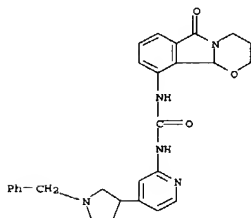


RN 322687-92-3 CAPLUS
 CN Urea, N-2-pyridinyl-N'-(3,4,6,10b-tetrahydro-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)-(9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

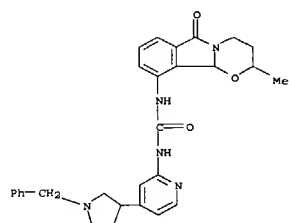


RN 322688-26-6 CAPLUS
 CN Urea, N-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]-N'-(3,4,6,10b-tetrahydro-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)-(9CI) (CA INDEX NAME)

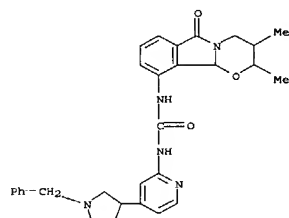


RN 322688-34-6 CAPLUS
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L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

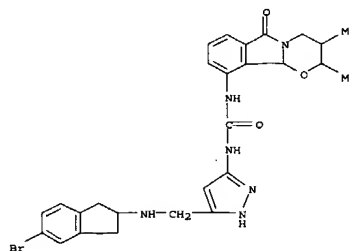


RN 322688-35-7 CAPLUS
 CN Urea, N-[(1S,4R,4aR,12aS)-1,3,4,4a,5,6a,11,12a-octahydro-11-oxo-1,4-methano-2H-isoindolo[2,1-a][3,1]benzoxazin-7-yl]-N'-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



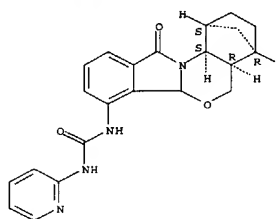
RN 322690 03-9 CAPLUS
 CN Urea, N-[(1S,4R,4aR,12aS)-1,3,4,4a,5,6a,11,12a-octahydro-11-oxo-1,4-methano-2H-isoindolo[2,1-a][3,1]benzoxazin-7-yl]-N'-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 445431-59-4 CAPLUS
 CN Urea, N-[(1S,4R,4aR,12aS)-1,3,4,4a,5,6a,11,12a-octahydro-11-oxo-1,4-methano-2H-isoindolo[2,1-a][3,1]benzoxazin-7-yl]-N'-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]- (9CI) (CA INDEX NAME)

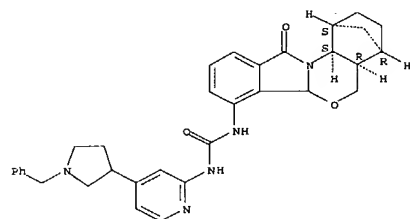
Absolute stereochemistry.



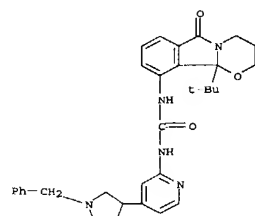
RN 445431-64-1 CAPLUS
 CN Urea, N-[(1S,4R,4aR,12aS)-1,3,4,4a,5,6a,11,12a-octahydro-11-oxo-1,4-methano-2H-isoindolo[2,1-a][3,1]benzoxazin-7-yl]-N'-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

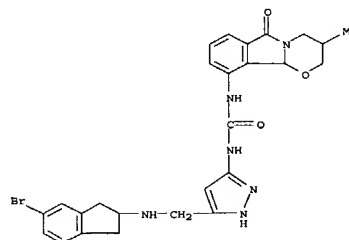


RN 445431-68-5 CAPLUS
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RN 445432 09-7 CAPLUS
 CN Urea, N-[(1S,4R,4aR,12aS)-1,3,4,4a,5,6a,11,12a-octahydro-11-oxo-1,4-methano-2H-isoindolo[2,1-a][3,1]benzoxazin-7-yl]-N'-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]- (9CI) (CA INDEX NAME)

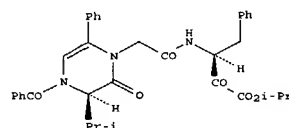
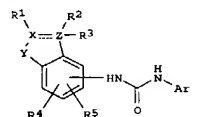
L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:78363 CAPLUS
 DOCUMENT NUMBER: 134:147614
 TITLE: Preparation of N,N'-biaryllurea derivatives as inhibitors of cyclin-dependent kinases (Cdk4 and Cdk6)
 INVENTOR(S): Hayama, Takashi; Hayashi, Kyoko; Honma, Mitsutaka; Takahashi, Ikuko
 PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 460 pp.
 DOCUMENT TYPE: CODEN: PIXXD2
 LANGUAGE: Patent
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION: Japanese

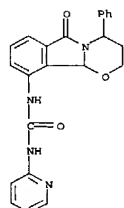
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007411	A1	20010201	WO 2000-JP4991	20000726
W:	AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, KG, KR, KZ, LC, LX, LR, LT, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	OH, OM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
JP 2001106673	A2	20010417	JP 2000-274175	20000726
EP 1199306	A1	20020424	EP 2000-949909	20000726
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
PRIORITY APPL. INFO.:			JP 1999-211384	A 19990726
			WO 2000-JP4991	W 20000726
OTHER SOURCE(S):			MARPAT 134:147614	
GI				

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

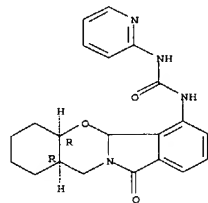


AB N-(hetero)aryl-N'-heterocyclylurea deriva. represented by general formula (I) [wherein Ar represents a nitrogenous heterocyclic aromatic group such as (un)substituted pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyrrolyl, imidazolyl, indolyl, isoindolyl, quinolyl, isoquinolyl, benzothiazolyl, or benzoxazolyl; X and Z each represents C or N or together with R1 or R2 and/or R3 represent CH or N; Y represents CO, SO, or SO2; R1 represents hydrogen, (un)substituted lower alkyl, Y3-W2-Y4-R5, etc.; wherein R5 = H, (un)substituted lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, aryl, imidazolyl, isoxazolyl, isoquinolyl, isoindolyl, indazolyl, indolyl, indolidinyl, isothiazolyl, ethylenedioxyphenyl, oxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, quinoxalyl, quinolyl, etc.; W2 = single bond, O, S, SO, SO2, N-(un)substituted NH, SO2NH, NHO2NH, NHO2, CONH, NHCO, NHCONH, NHCO2, etc.; Y3, Y4 = single bond, linear or branched lower alkylene; R2 and R3 each represents hydrogen, lower alkyl or alkoxy, or Y3-W2-Y4-R5 (Y3, W2, Y4, R5 = same as above), or one of R2 and R3 together with R1 and X forms cyclohexane, cyclopentane, piperidine, 3,4,5,6-tetrahydro-1,3-oxazine, tetrahydrothiopyran, pyrrolidine, tetrahydrothiofuran, oxazolidine ring, etc.; R4 and R5 represent H, halo, OH, amino, or Y3-W2-Y4-R5 (Y3, W2, Y4, R5 = same as above) or salts thereof are prepared. The compds. (e.g. II) have a remarkable proliferation-inhibitory effect on tumor cells. A Cdk4 and/or Cdk6 inhibitor for use in the therapy of malignant tumor can hence be provided. II showed IC50 of 0.061 and 0.019 μM against cyclin-D1-Cdk4 and cyclin-D2-Cdk4, resp., vs. 0.36 and 0.056 μM, resp., for (±)-flavopiridol, and inhibited the proliferation of HCT116 and MKN-1 cells with IC50 of 0.013 and 0.10 μM, resp., vs. 0.15 and 0.87 μM, resp., for (±)-flavopiridol. Pharmaceutical formulations containing I were prepared.

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 IT 322687-73-0P 322687-74-1P 322687-75-2P
 322687-92-3P 322688-08-4P 322688-09-5P
 322688-10-8P 322688-16-6P 322688-18-8P
 322688-29-9P 322688-34-6P 322688-35-7P
 322690-03-9P 322690-04-0P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of N-(hetero)aryl-N'-heterocyclylurea derivs. as in inhibitors of cyclin-dependent kinases (Cdk4 and Cdk6) and antitumor agents)
 RN 322687-73-0 CAPLUS
 CN Urea, N-2-pyridinyl-N'-(3,4,6,10b-tetrahydro-6-oxo-4-phenyl-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)

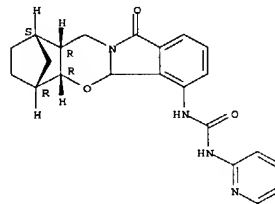


RN 322687-74-1 CAPLUS
 CN Urea, N-[(5aR,9aR)-4b,5a,6,8,9,9a,10,12-octahydro-12-oxo-7H-isoindolo[1,2-b][1,3]benzoxazin-4-yl]-N'-2-pyridinyl- (9CI) (CA INDEX NAME)
 Absolute stereochemistry.

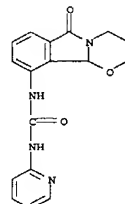


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L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 RN 322687-75-2 CAPLUS
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 Absolute stereochemistry.



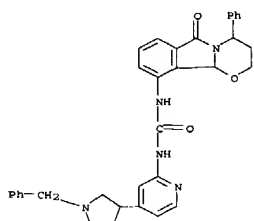
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RN 322688-08-4 CAPLUS
 CN Urea, N-[4-[(1-phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]-N'-(3,4,6,10b-tetrahydro-6-oxo-4-phenyl-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)

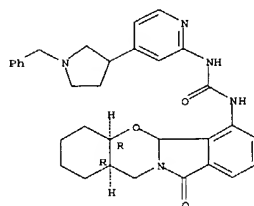
04/07/2004

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 322688-09-5 CAPLUS
 CN Urea,
 N-[(5aR,9aR)-4b,5a,6,8,9,9a,10,12-octahydro-12-oxo-7H-isoindolo[1,2-b][1,3]benzoxazin-4-yl]-N'-[4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl]- (9CI) (CA INDEX NAME)

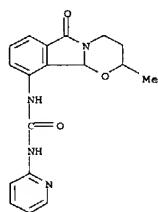
Absolute stereochemistry.



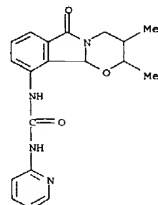
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Absolute stereochemistry.

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

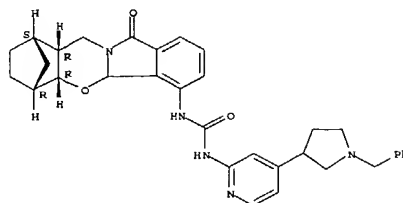


RN 322688-29-9 CAPLUS
 CN Urea, N-2-pyridinyl-N'-[(3,4,6,10b-tetrahydro-2,3-dimethyl-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)

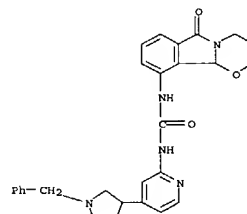


RN 322688-34-6 CAPLUS
 CN Urea, N-4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl-N'-[(3,4,6,10b-tetrahydro-2-methyl-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

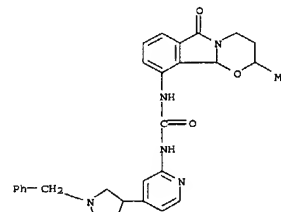


RN 322688-26-6 CAPLUS
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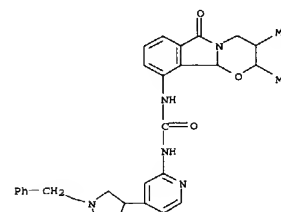


RN 322688-28-8 CAPLUS
 CN Urea, N-2-pyridinyl-N'-[(3,4,6,10b-tetrahydro-2-methyl-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



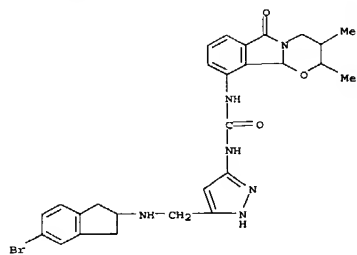
RN 322688-35-7 CAPLUS
 CN Urea, N-4-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinyl-N'-[(3,4,6,10b-tetrahydro-2,3-dimethyl-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)



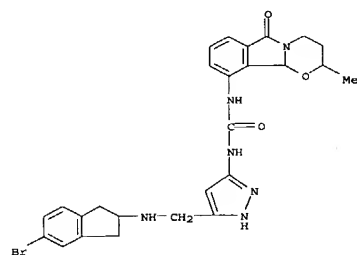
RN 322690-03-9 CAPLUS
 CN Urea,
 N-[5-[[[5-bromo-2,3-dihydro-1H-inden-2-yl]amino]methyl]-1H-pyrazol-3-yl]-N'-[(3,4,6,10b-tetrahydro-2,3-dimethyl-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 322690-04-0 CAPLUS
CN Urea,
N-[5-[[[5-bromo-2,3-dihydro-1H-inden-2-yl]amino]methyl]-1H-pyrazol-3-yl]-N'-(3,4,6,10b-tetrahydro-2-methyl-6-oxo-2H-[1,3]oxazino[2,3-a]isoindol-10-yl)- (9CI) (CA INDEX NAME)



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